DETAILED ACTION

Applicant's election of the elected compound, field on 11/13/2007 is acknowledged. Because Applicant did not distinctly and specifically point out supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 5-17; 30-32; 34-36; 38-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. The requirement is still deemed proper and is therefore made FINAL.

Accordingly, no claims have been added, amended or cancelled.

Claims 1-4; 18-29; 33; 37 are presently under examination and are the subject of this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4; 18-29;33; 37_are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of controlling proliferative cells in a subject.

The breadth of the claims

The claims encompass the treatment in vivo of a patient with human breast ductal adenocarcinoma.

The unpredictability of the art and the state of the prior art

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4)

teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro)*. Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

In addition, the treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp. 1041-1042) who discusses the potential shortcomings

of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Working examples

The specification provides a single working example of administering the elected compound to breast cancer cells (example 1 in specification)

Guidance in the specification

The specification of the instant application provides little guidance in terms treating patients comprising the administration of the elected compound for the in vivo treatment of human breast ductal adenocarcinoma. In view of the unpredictable nature of treating cancer in general and the lack of correlation between in vitro experimentation and in vivo predictability, the lone working example is insufficient to guide or teach one of skill in the art how to use the instant invention.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that ad, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4; 18-29; 33; 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Flescher et al. (US Patent 6,469,061) in view of Landgraf et al. (European Journal of Plant Pathology, 108: 279-283, 2002).

Flescher et al. teach of a pharmaceutical composition useful for the treatment of cancer in mammals, comprising as the active ingredient a therapeutically effective amount of a jasmonate (see abstract). The invention discloses use of members of the plant stress hormone family termed "jasmonates" for suppressing and killing mammalian cancer cells that represent major types of human malignancies (column 2, last paragraph). Further, Applicant disclose that given

chemotherapeutic agents mechanism of action involves induction of apoptosis in cancer cells, and since jasmonates are also thought to be involved in an apoptotic response to plant stress, the applicants tested the ability of jasmonates to suppress replication of mammalian cancer cell lines. In particular, the invention is also effective toward the treatment of breast cancer (see claim 28). The reference does not teach the compound elected by Applicants.

Landgraf et al. teach that the elected compound, 12-oxo-phytodienoic acid (OPDA) is a precursor to jasmonate (page 279, column 2, second paragraph).

It would be obvious to one of ordinary skill in the art would have been motivated to combine the teachings of Flescher et al. and Landgraf et al. One would have been motivated to do so since the elected compound, is a biological precursor to a compound already know to be an effective treatment for cancer, in particular breast cancer. Thus, jasmonate and the elected compound, 12-oxo-phytodienoic acid, are biologically related compounds. Additionally, the administration and specific source of a compound (such as in the same formulation, different formulations, same route, different routes, orally, intravenously, simultaneously, sequentially etc.) is well within the knowledge of the skilled artisan to determine how and what formulation combination and mode of administering will be appropriate for the patient, which will depend on the type of cancer.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

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